Case Report

Combined salvage ibrutinib/rituximab therapy in chronic lymphocytic leukemia (del17p) with autoimmune cytopenias - case report

Summary

We present a case report of ibrutinib treatment combined with RCD scheme (rituximab, cyclophosphamide and dexamethasone) due to persistent symptoms of autoimmune cytopenia in a patient with chronic lymphocytic leukemia with 17 p deletion. The patient was diagnosed in 2004 and received 5 lines of chemotherapy before ibrutinib. In 2010 the autoimmune cytopenia (AIHA) with haemolytic anemia Coombs positive and thrombocytopenia (IT) was diagnosed. Ibrutinib has started in November 2014. The improvement of mood was observed already after the first 2 months, partial regression of nodal lesions, spleen and liver enlargement during 9 months of treatment. The use of ibrutinib did not affect the course of AIHA and IT. RCD were used concomitantly with ibrutinib and the disappearance of all the symptoms of AIHA and IT was observed..6 RCD cycles were administered.. No toxicity was observed in combination therapy. Symptoms of AIHA and IT never recurred, even at the time of the progression of the disease after 45 months of treatment with ibrutinib. The patient died due to the progression of the disease (despite the use of venetoclax) complicated by pleural empyema, 14 years after first diagnosis.

Keywords: ibrutinib, autoimmune cytopenias, CLL

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Introduction

Chronic lymphocytic leukemia is the most common adult leukemia, rarely occurring to young people under 50 years of age (1, 2). The quality of life of patients with advanced disease may be poor due to troublesome weakness, recurrent opportunistic infections, and finally frequent indications for blood or platelet transfusions.[1–3] The patients often had autoimmune complications. The most common (5-10%) is autoimmune haemolytic anemia (AIHA) and immunological thrombocytopenia (IT).[4] Patients with 17 p-deletion have worse prognosis as to survival time and response time to subsequent treatment lines.[1–3] Autoimmune cytopenias are diagnosed in patients observed over many years of therapy. Recently, only alemtuzumab[2] was the treatment of choice in this group of patients, nowadays thanks to drugs such as BCR-dependent kinase inhibitors (ibrutinib, idelalisib), BCL2 ventoclax inhibitor, anti-CD20 antibodies (obinuntuzumab, ofatumab) and combined therapy the progression free survival and quality of life of these patients are better. For patients who have been treated for many years, new particles may only have the character of an salvage therapy, where the chances of long-term response still seems to be uncertain.[5] The diagnose of autoimmune cytopenias strongly differs from the population with extensive bone marrow infiltration only.[4,6,7] In the treatment of cytopenia symptoms, cyclophosphamide and rituximab (anti CD20+ antibody (4)) may be used in addition with corticosteroids. There is now more and more data on autoimmune cytopenia in the context of new drugs, [6,7] but as in the RESONATE study,[8] the evaluation concerned the comparison of the occurrence of these symptoms as a complication in the treatment with ibrutinib or of atumumab. There are small data concerning management of autoimmune cytopenias in CLL in novel therapy era, especially in suboptimal response in autoimmune complications.

Case report

In 2004 the diagnosed of chronic lymphocytic leukemia based on peripheral blood flow cytometry was done. There was no “watch and wait” phase because of clinical symptoms: anemia, weakness and bulky lymphadenopathy from the beginning of the disease. Stage III in modified Rai classification.

First line treatment was chlorambucil monotherapy through one year, partial response was achieved, leukocytosis fell down to 40 thousand (10% neutrophils) lymph nodes reduction to 15 mm.

In 2006 patient has progressed: massive lymphadenopaty occured. Deletion 17p on 63% cells was found. Second line therapy was fludarabin with alemtuzumab. She received 6 courses and achieved partial response showing remission of lymphadenopaty and improvement of blood parameters which lasted 2,5 years. During this treatment she had twice severe respiratory infection. Persistent anemia and thrombocytopenia caused often transfusions. . In 2010 the autoimmune cytopenia (AIHA) with haemolytic anemia Coombs positive and thrombocytopenia (IT) was diagnosed.

Since 2009 to 2011 there was no treatment, but the progressive weakness and rising leukocytosis was observed. She started R-CVP/CVP ongoing till 2013 with many intervals. It was interrupted by frequent infections, transfusions, also due to patient’s decision - patient disliked to receive chemotherapy. In 2013/2014 bendamustin as salvage therapy was applied. There was no response neither improving quality of life nor symptoms of disease. In October 2014 the patient was average general condition ECOG 2, anemia, consul’s neck, axillary lymph nodes 4 cm, inguinal lymph nodes 3 cm, extensive enlargement of spleen and liver. Leukocytosis 200

thousand, hemoglobin 8,8 g%, platelets 60 thousand, creatinine and liver tests normal; LDH, B2 microglobulina and CRP 3 times above normal.

The patient started ibrutinib in 27 NOV 2014. After two months there was improvement of quality of life, ECOG 1. Typical increase of leucocytosis (to 263 thousand) was observed till February 2015. Patient took pills regularly in adequate dose. Anemia and thrombocytopenia have remained unchanged. Transfusions were done regularly. Anemia occurred suddenly with fever and chills. The bacterial and viral infections as a reason of incidents of hemolysis were excluded. The level of hemoglobin was decreasing even lower than 5 g% (drop down from 8-9 g%). She required transfusions, frequent additional medical care. Prednisolone didn't control the symptoms (Table 1).

Table 1 Example of laboratory studies before start and at time of better response during ibrutinib

	Before ibrutinib September 2014	**Best response on ibrutinib September 2017**
WBC G/l	158	26,02
% lymphocytes	87,9	63%
Erythrocytes T/l	3,13	4,33
Platelets G/L	30	111
Flow Cytometry immunophenotype %	CD5 -72,	CD5-95,5
	CD19-94,9	CD19- 87
	CD 20- brak	CD20-46
	CD23 -40	CD23-62,3
	CD10-negative	CD10-<0,1
	Lymphocyte 94%	Lymphocyte- 74,3%
	Subpopulation I- 75%,	Subpopulation I- 75,41%,
	Subpopulation III- 10%	Subpopulation III-1,75%

Thrombocytopenia level never reached more than 30 thousand. The autoimmunologic cytopenias was confirmed: typical clinical manifestation with hemolysis, no progression of bone marrow infiltration, nor other symptoms of disease. Ibrutinib treatment allowed to achieve partial regression, but without improvement of autoimmunologic cytopenia. On May 2015 cyclophosphamide, rituximab and dexamethasone (RCD) were added. Six cycles of RCD were prescribed and resulted the normalization of hemoglobin level and platelets level. Adding RCD to ibrutinib did not cause any side effects. There was no need to do more transfusions. After 9 months of ibrutinib treatment no peripheral lymphadenopathy was detected, liver and spleen had normal size. The patient gained weight. At that time leukocytosis were 104 thousand, platelets 106 thousand, hemoglobin 9 g%. The ibrutinib monotherapy was continued. The quality of life improved: no infections, nor other side effects. Peripheral blood flow cytometry was performed – 63% cells with phenotype CD19+/5+/23+/200+ (27,6 %) lub CD19+/5+/23-/200+. (36,3%). Frequency of visits have been reduced. From the beginning of 2016 there was ongoing improvement in quality of life and lymphadenopathy despite the level of leukocytosis (35,0 u/l). The patient felt healthy. The treatment has been conducted from NOV 2013 until SEP 2018 when rapid progression occurred. Richter syndrome wasn't confirmed. During first two weeks of venetoclax prescribe severe lysis syndrome was observed. The second cycle was complicated by pleural empyema. Despite of treatment she died on DEC 2018.

The simultaneous use of ibrutinib with rituximab, cyclophosphamide and dexamethasone-resulted in the permanent resolution of autoimmune symptoms. No complications of the treatment have been observed. This case is an example of 14 years treatment a patient with chronic lymphatic leukemia and autoimmune cytopenias in terms of the use of ibrutinib.

Comments

Clinical course of chronic lymphocytic leukemia comes from the times when there was no effective therapy. Patients received anticancer treatment late, at the time of very severe symptoms of the disease, when the tumor mass was high, and a loss of immunity was also observed. This strategy resulted in more side effects during therapy as opportunistic infections which were the most common cause of death in CLL patients.[1–3] In recent years, the value of several new drugs from the family of anti-CD20 monoclonal antibodies Obinuntuzumab, Ofatumab as well as signal-to-receptor (BCR) inhibitors, including Bruton kinase inhibitor (BTK) ibrutinib, idelalisib inhibitor PI3K,[5–8] antiapoptotic protein antagonist BCL-2 (venetoclax) has been demonstrated.[9]

The group of patients treated for many years before new drug era, as our patient, is a different population of patients. They often have the complications of previous therapies,. The management of such a case must be individualized and taken into account not only the treatment of disease progression, but also the adverse events after previous therapies. In the PYC-1102[6] study, where the drug was used in patients with refractory disease, 88% of responses were obtained, including 2% of total remissions, 68% of partial responses and 18% of partial responses with lymphocytosis. Our patient represented the case of partial response with lymphocytosis. In this study the percentage of PFS and OS was 76% and 83% respectively after 26 months of observation, and the response was not dependent on p53 mutation or the presence of 17 p(5. 6) deletion. Our patient had a 45-month response to the treatment.

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Ibrutinib was used in fifth line. The subjective improvement came quickly, nodal regression during few months, but the symptoms of AIHA and IT have not disappeared. A supplementation with blood products was necessary. A symptoms was particularly troublesome for the patient and worsening the quality of life. They did not improve despite the clinical effect of ibrutinib. In previous reports[4,10,11] it was suggested that the use of ibrutinib is effective in the treatment of immunological cytopenia. Although novel therapies such as ibrutinib, idelalisib, venetoclax have been shown to be effective in CLL therapy, no clinical trials have studied the novel signal inhibitors in the management of autoimmune cytopenias in CLL. The efficacy of ibrutinib in controlling autoimmune cytopenias was studied by Vitale[13] in the retrospective group of 13 patients. 15% (2 patients) required cytopenia treatment regardless of treatment with ibrutinib. After improvement the symptoms of cytopenia they continued treatment with ibrutinib, without recurrence of cytopenia.

Diagnosis of autoimmune cytopenias can be challenging, in our patient the autoimmunity as a reason of anemia and thrombocytopenia wasn't in any doubt. Evidence regarding treatment of secondary autoimmune cytopenias is limited, many options exist.[13,14] Traditional therapy of autoimmune complications in CLL consists of immunosuppression with corticosteroids and anti CD20 monoclonal antibodies. The use of the RCD scheme for the treatment of AIHA and IT (12) resulted in the resolution of symptoms in our patient.

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Conflicts of interest

The author declares no conflicts of interest.

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